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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/727,198

11/30/2000

Pierre L. Triozzi

CIR 2-005

2840

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7590

05/25/2006

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EXAMINER

WINKLER, ULRIKE

ART UNIT

PAPER NUMBER

1648

DATE MAILED: 05/25/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/727,198

Applicant(s)

TRIOZZI ET AL.

Examiner

Ulrike Winkler

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 March 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8 and 57-66 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8, 57-66 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The Amendment filed March 9, 2006 in response to the Office Action of September 30, 2005 is acknowledged and has been entered. Claims 1-8, 57-66 are pending and are currently being examined.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

The prosecution history of this application is as follows:

- (1) An Election/Restriction requirement was mailed on February 22, 2002.
- (2) Applicants filed a response on March 22, 2002 traversing the Restriction requirement.
- (3) A first Office action was issued on June 18, 2002. The restriction requirement at that point was essentially maintained. A double patent rejection and a 35 USC §102 rejection were made in the action.
- (4) Applicants filed a response to the Office action on December 23, 2002.
- (5) A Final Office action was issued on March 11, 2003. In view of Applicants amendments to the claims Groups 1, 2, 13 and 15 were rejoined at that time. The double patent rejection and a 35 USC §102 rejection were maintained.
- (6) Applicants filed their first after Final Response on June 25, 2003.
- (7) An After Final Rejection was issued by the Office on July 21, 2003 for reasons set out in the final office action.

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(8) An Interview was held on August 4, 2003 with Applicants representative. Suggestions were made for the purpose of claim clarification. There is no indication in any part of the interview summary that the claims would be allowable in view of the suggested claim amendments.

(9) Applicants filed their second after Final Response on August 7, 2003.

(10) An After Final Rejection was issued by the Office on September 8, 2003. The amendments filed August 7, 2003 were not entered. The claim amendments did not make the claims allowable. The claim amendments changed the description of the product and cast the product in the form of a product-by-process format. Product-by-process claims are interpreted as products and are rejected based on comparison of the product composition and not on how the products are made.

(11) A request for an RCE was filed on November 7, 2003.

(12) A non-final Office action was issued on September 30, 2005. The restriction requirement at that point was essentially maintained. A double patent rejection and a 35 USC §102 rejection were maintained in the action.

(13) Applicants filed the instant response on March 9, 2006.

Applicants' assert is that they have complied with the suggestions made the advisory action July 21, 2003 and interview of August 4, 2003. In response, although, applicants' claims have been recast as product-by-process, the claims remain interpreted as being drawn to products. As such the claims have been rejected in view of the cited art. The office apologizes if applicants inferred from the prior communications that the claims as presented are allowable. However, the claims are now product-by-process claims and are treated as products. The products are found in

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the prior thus as products they are not allowable. Applicants' arguments and the examiners response are essentially the same as those of record.

Double Patenting

The rejection of Claims 1-8 and 57-66 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 11, 12, 14, 17 and 18 of U.S. Patent No. 6,093,381 **is maintained** for reason of record. The rejection is evidenced by Triozzi et al. (AIDS Research and Human Retrovirus, 1998).

Applicants arguments are that the presence of components less than 50 kDa is detrimental to the activity of the factor. Applicants have chosen to (1) exclude the components of factors less than 50 kDa, and (2) the use of the factors greater than 50 kDa resulted in superior results. Applicants arguments are not convincing because the supernatant in the U.S. Patent No. 6,093,381 can be shown by the Triozzi et al. (AIDS Research and Human Retrovirus, 1998) to contain the IL12 and TNF- α mRNA expressed products. Furthermore, IL-12 has been purified because the sequence is known.

In response purified product may be considered new for the purpose of meeting 101 requirements, they may never the less be unpatentable for lack of invention as being obvious under 103. See *In Re Bergstom and Sjoval*, 166 USPQ 256 (CCPA 1970)

The instant invention is drawn to a product (a factor). The product-by-process claims are interpreted as "a composition of matter" (which are *products*, wherein the chemical nature of the substances or materials used. A composition may be a molecule, compound, solution, mixture,

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alloy, atom, etc.). Product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims are directed at treating a patient afflicted with a disease - cancer- comprising a greater than 50 kDa fraction of a supernatant from mitogenically stimulated lymph node lymphocytes. The factor is obtained from cells stimulated with IL-2 and anti-CD-3 Ab. The patented claims are drawn to a whole supernatant fraction from lymph node cells stimulated with IL-2 and anti-CD-3 Ab. The patented claims are drawn to improving the treatment of cancer patients utilizing this supernatant which inherently contains the greater than 50 kDa fraction. The limitation of "treating patients" is broad and includes combination therapies as found in claims 11, 12, 14, 17 and 18 of U.S. Patent No. 6,093,381. Triozzi et al. (AIDS Research and Human Retrovirus, 1998) teaches that mRNA is expressed in lymph node cells that have been treated with IL2 and anti-CD3 antibody, like the lymphocytes in U.S. Patent No. 6,093,381. IL12 and TNF- α mRNA is expressed in these treated cells. IL-12 is a heterodimer protein with a molecular mass of 57.2 kDa in unglycosylated form and 75 kDa in glycosylated form. TNF- α is a multimeric protein that forms trimers, the single unit of TNF is approximately 17 kDa in size and the trimer is approximately 51 kDa in size. Therefore, the instant rejection is maintained.

Claim Rejections - 35 USC § 102

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The rejection of claims 1-8 and 57-66 under 35 U.S.C. 102(a) or 35 U.S.C. 102(e) as being anticipated by Triozzi et al. (U.S. Pat. No. 6,093,381) **is maintained** for reasons of record. The rejection is evidenced by Triozzi et al. (AIDS Research and Human Retrovirus, 1998).

Applicants arguments are that the presence of components less than 50 kDa is detrimental to the activity of the factor. Applicants have chosen to (1) exclude the components of factors less than 50 kDa, and (2) the use of the factors greater than 50 kDa resulted in superior results. Applicants arguments are not convincing because the supernatant in the U.S. Patent No. 6,093,381 can be shown by the Triozzi et al. (AIDS Research and Human Retrovirus, 1998) to contain the IL12 and TNF- α mRNA expressed products. Furthermore, IL-12 has been purified because the sequence is known.

The claims are directed at lymphocytes derived from lymph node or peripheral blood. There is not objective evidence on the record that these cell populations actually behave differently in response to IL-2 and anti-CD3 treatment.

Triozzi et al. (AIDS Research and Human Retrovirus, 1998) teaches that mRNA is expressed in lymph node cells that have been treated with IL2 and anti-CD3 antibody, like the lymphocytes in U.S. Patent No. 6,093,381. IL12 and TNF- α mRNA is expressed in these treated cells. IL-12 is a heterodimer protein with a molecular mass of 57.2 kDa in unglycosylated form and 75 kDa in glycosylated form. TNF- α is a multimeric protein that forms trimers, the single unit of TNF is approximately 17 kDa in size and the trimer is approximately 51 kDa in size. Therefore, the instant rejection is maintained.

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The rejection of claims 1, 5, 57 and 61 under 35 U.S.C. 102(b) as being anticipated by Chang et al. (U.S. Pat. No. 4,596,774) **is maintained** for reasons of record.

Applicant's response has been fully considered but is not deemed persuasive for the reason set out in the previous rejection. Applicant's arguments essentially are that the claims are limited to the process steps leading to the greater than 50 kDa fraction. However, the amendments are drawn to a product (a factor) made by a process. The amended claims does not distinguish over the prior art (Change et al.), which fractionated (isolated) the supernatant of stimulated cells on an SDS page gel (see figure 5). Thus the reference teaches an isolated factor (a composition) that is greater than 50 kDa in size on SDS-Page gel. Chang et al. disclose the methods of preparing cell-free products (supernatant) from stimulated peripheral blood lymphocytes. The supernatant contains all molecular weight fractions including those that are greater than or equal to 50 kDa (see figure 5). The reference discloses using the supernatant as a treatment. Therefore, the rejection is maintained.

The rejection of claims 1-8 and 57-66 under 35 U.S.C. 102(b) as being anticipated by Triozzi et al. (AIDS Research and Human Retrovirus, 1998) **is maintained** for reason of record.

Applicants' arguments are that the presence of components less than 50 kDa is detrimental to the activity of the factor. Applicants have chosen to (1) exclude the components of factors less than 50 kDa, and (2) the use of the factors greater than 50 kDa resulted in superior results. Applicants arguments are not convincing because the supernatant of Triozzi et al. contains the IL12 and TNF- α mRNA expressed products. Furthermore, IL-12 has been purified because the sequence is known.

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The claims are directed at lymphocytes derived from lymph node or peripheral blood. There is not objective evidence on the record that these cell populations actually behave differently in response to IL-2 and anti-CD3 treatment.

The rejection is maintained because the reference discloses that mRNA is expressed in lymph node cells that have been treated with IL2 and anti-CD3 antibody. IL12 and TNF- α mRNA is expressed in these treated cells. IL-12 is a heterodimer protein with a molecular mass of 57.2 kDa in unglycosylated form and 75 kDa in glycosylated form. TNF- α is a multimeric protein that forms trimers, The single unit of TNF is approximately 17 kDa in size and the trimer is approximately 51 kDa in size. Thus, the instant reference anticipates the instant invention.

The rejection of claims 1-8, 57-66 under 35 U.S.C. 102(b) as being anticipated by Tanaka et al. (EMBO Journal, 1995) is **maintained** for reasons of record.

Applicants' argument was that the specification has specifically pointed out that sFasL is not an active component of the factor. The claims as written do not specifically exclude the sFasL component. Thus the claims still read on sFasL. Applicant may amend the claims to specifically exclude sFasL provided there is written description in the specification for the negative limitation.

The claims are directed at lymphocytes derived from lymph node or peripheral blood. There is not objective evidence on the record that these cell populations actually behave differently in response to IL-2 and anti-CD3 treatment.

Tanaka et al. disclose mitogen stimulated peripheral blood T lymphocytes for preparing a cell-free product: sFasL. The reference discloses that sFasL forms trimers and therefore achieves

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a size greater than the monomeric 40 kDa membrane form (greater than 50Kda). FasL association with Fas results in the activation of apoptosis leading to cell death and any cell that carries Fas is susceptible to this death pathway. Therefore, the instant invention is anticipated by Tanaka et al.

The rejection of claims 1, 2, 5, 6, 57, 58, 61 and 64-66 are rejected under 35 U.S.C. 102(b) as being anticipated by Mire-Sluis et al. (Cytokines, 1998, pp. 183-203, 217-219, 227-230, 245-260, 277-296, 335-360, 526-546) **is maintained** for reason of record.

The instant invention is drawn to a product (a factor). The product-by-process claims are interpreted as “a composition of matter” (which are *products*, wherein the chemical nature of the substances or materials used. A composition may be a molecule, compound, solution, mixture, alloy, atom, etc.). Product-by-process claims are not limited to the manipulations of the recited steps, only to the structure implied by the steps. M.P.E.P. Section 2113 states that:

“[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985) (citations omitted)

The claims are directed at lymphocytes derived from lymph node or peripheral blood. There is no objective evidence on the record that these cell populations actually behave differently. Thus if a composition has been purified in one type of lymphocyte it is presumed to be present in the other type of lymphocyte as well.

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Mire-Sluis et al. disclose IL-12 that is a heterodimeric protein. The protein backbone has a molecular mass of 57.2, although the glycosylated protein approximately 70 kDa as determined by analytical ultracentrifugation (see page, 186, 189, 532).

The reference discloses IL-14 which has a molecular mass of 53.1 kDa and is produced by normal T-cell, T cell clones and T cell lineage as well as B-cell lineage lymphoma cell lines (see page 218, 533).

The reference discloses IL-16 is a homotetramer having a molecular mass 56 kDa (see page 227, 534).

The reference discloses MCSF has a molecular mass of 45-90 kDa and is derived from T-cells (see page 247, 249, 537).

The reference LIF has an apparent molecular mass of 32-67, the LIF is produced and secreted by a wide variety of cells upon stimulation (see pages 278, 280, 238).

The reference teaches TNF and lymphotoxin (LF). The TNF and LF subunits have a molecular mass of 17 kDa and 25 kDa. TNF and LF form homotrimers that have a molecular mass 51 kDa and 75 kDa. Trimers are the biologically active form of TNF and LF. (see pages 339, 340, 541)

Therefore, the instant invention is anticipated by Mire-Sluis et al.

Claim Rejections - 35 USC § 112

The rejection of claims 1-8 and 57-66 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention **is maintained** for reasons of record. Claims 1-8

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and 57-66 are indefinite in that they only describe the compositions of interest by an arbitrary name (a factor). Here applicants are claiming a composition (a factor) by claiming the composition as a particular fraction of the supernatant of an activated lymphocyte. While the name itself may have some notion of the activity of the protein, there is nothing in the claims that distinctly claims the factor. For example, others in the field may isolate the same protein (factor) and have giving the protein such an entirely different name (e.g., IL12, IL16, MCSF, TNF, LF, sFasL). Applicant should particularly point out and distinctly claim the composition by claiming characteristics associated with the factor (e.g. activity, molecular weight, amino acid composition, N-terminal sequence, etc.). Here Applicants are attempting to narrow the supernatant fraction to only claiming those proteins in the fraction that comprise compositions greater than 50 kDa, however, the prior art has shown that lymphocyte produce many cytokines that may fall within the claimed factor and they have not sufficiently defined their composition from those in the prior art. Claiming biochemical molecules by a particular name given to the protein by various workers in the field fails to distinctly claim what that protein is and what the compositions are made up of. In consideration of the discrepancies often encountered in the art between protein molecular weight when determined by different methods, when a molecular weight is recited to characterize a protein (or a composition) the claims should include not only the method by which it was determined, e.g. whether by SDS-Page gel electrophoresis, gel filtration or some other method, but also whether the determination was made under denaturing or non-denaturing conditions and whether reducing or non-reducing conditions were used.

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Conclusion

No claims allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

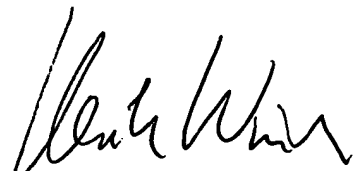
Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989). The Group 1600 Official Fax number is: (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Tech Center representative whose telephone number is (571)-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ulrike Winkler, Ph.D. whose telephone number is 571-272-0912. The examiner can normally be reached M-F, 8:30 am - 5 pm. The examiner can also be reached via email [ulrike.winkler@uspto.gov].

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph.D., can be reached at 571-272-0974.


ULRIKE WINKLER, PH.D.
PRIMARY EXAMINER 5/23/06